

Next-generation tools to tackle relapses

Historically, global efforts to tackle malaria have focused primarily on *Plasmodium falciparum* malaria, due to its higher disease burden and associated health risks, including death – particularly among children. Conversely, *Plasmodium vivax* malaria is often neglected, despite having the widest geographical distribution of the five species of parasite affecting humans.

P. vivax accounts for around half of the malaria cases outside sub-Saharan Africa and is often the predominant species of malaria in countries that are close to eliminating the disease.¹ It threatens around 2.5 billion people and causes around 7.5 million clinical infections every year,² many of which are relapses of existing infections that occur in the absence of new infective mosquito bites. This occurs because *P. vivax* parasites can lie dormant in the liver in a form known as hypnozoites, which can reactivate weeks, months or even years after the initial infection.

Until recently, primaquine (PQ) was the only available treatment for the prevention of *P. vivax* relapses. However, patients often do not comply with the WHO-recommended 14-day treatment regimen for PQ, leading to reduced efficacy. A more compact-dosing regimen to improve compliance was therefore urgently needed.

Tafenoquine: transforming the treatment of relapsing *Plasmodium vivax* malaria

In July 2018, MMV and its partner GSK celebrated a major milestone: tafenoquine (TQ), a single-dose medicine, became the first new treatment to prevent relapses of *P. vivax* malaria since the approval of PQ in 1952. TQ was approved (as *Krintafel*³) by the US Food and Drug Administration for “the radical cure (prevention of relapse) of *P. vivax* malaria in patients aged 16 years and older who are receiving appropriate antimalarial therapy for acute *P. vivax* blood-stage infection.”⁴ In September 2018, a second stringent regulatory authority, the Australian Therapeutic Goods Administration, also approved TQ (as *Kozenis*⁵) for the same indication,⁵ paving the way for regulatory submissions and review in malaria-endemic countries.

Both PQ and TQ belong to the same class of compounds (the 8-aminoquinolines). Because the 8-aminoquinolines can cause haemolysis in individuals who are deficient in the enzyme glucose-6-phosphate dehydrogenase (G6PD), PQ and TQ are contraindicated in this patient population. To help identify patients who are eligible for treatment, MMV and GSK’s partner PATH, a non-profit global health organization based in Seattle, has supported the development of a quantitative point-of-care G6PD diagnostic tool – now approved in many countries, including Brazil, Thailand, Myanmar, Indonesia and India.

In 2018, regulatory filings for TQ occurred in Brazil, Colombia and India, with additional filings planned for 2019 in seven other countries across South America, South East Asia and the Horn of Africa. The focus is now on generating evidence to support the adoption of TQ and G6PD in national treatment guidelines, a precondition for ensuring patient access to these tools. Studies to assess the feasibility of providing appropriate radical cure (TQ or PQ) after quantitative G6PD testing, at different levels of the health services, are planned in Brazil, Thailand and Ethiopia. These studies, designed in close collaboration with the respective National Malaria Control Programmes (NMCPs), national experts and the WHO, should provide insight into how best to incorporate the new tools into the case management of *P. vivax* malaria.

MMV and PATH are engaging with Ministries of Health, NMCPs and key stakeholders in malaria-endemic countries to support national efforts to control and eliminate *P. vivax*. This work is supported in part by VivAccess, an initiative funded by the Bill & Melinda Gates Foundation, which aims to catalyse the adoption of TQ and new tools for the case management of *P. vivax*, including a more sensitive point-of-care diagnostic – currently under development. These tools have the potential to deliver both individual and public health benefits in terms of reduced relapses and onward transmission of *P. vivax*, contributing to its eventual elimination.

1 World Health Organization, Control and elimination of *Plasmodium vivax* malaria: a technical brief (2015): <http://apps.who.int/iris/handle/10665/181162>

2 World Health Organization, World Malaria Report 2018: <https://apps.who.int/iris/bitstream/handle/10665/275867/9789241565653-eng.pdf?ua=1>

3 Trademarks owned or licensed by GSK.

4 US FDA highlights of prescribing information: https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/210795s000lbl.pdf

5 The approval of TQ was based on efficacy and safety data from over 800 subjects treated with a single 300 mg dose of the drug in two key Phase III trials, published in January 2019: <https://www.nejm.org/doi/full/10.1056/NEJMoa1710775> (DETECTIVE) and <https://www.nejm.org/doi/10.1056/NEJMoa1802537> (GATHER). Historical data from 33 other studies, involving over 4,000 subjects exposed to varying doses of TQ, were also included in the regulatory submission.

Sri Lanka has successfully eliminated malaria. To what would you attribute this success?

→ Several factors, I would say. A key element was the leadership of the central anti-malaria campaign, which was complemented by a very effective team of regional malaria officers. Before and throughout the elimination phase, the country made sure that sound policies, effective implementation and coordination measures, as well as quality products and services, were in place to maximize the chance of success.

A rigorous monitoring and evaluation approach was also applied to the management of grants. Sri Lanka received grants from The Global Fund for its malaria elimination efforts, and I believe it was the ability to direct these funds where needed that made the difference, probably as much as the actual funding itself.

In South East Asia, *P. vivax* accounts for an increasing proportion of malaria cases. What do you see as the key challenges to the control and elimination of *P. vivax*?

→ One key challenge is preventing relapses. The current anti-relapse medication is PQ, a 14-day treatment course that can only be given after testing for G6PD activity because the drug can induce acute, life-threatening haemolysis in people deficient in this enzyme. In an ideal world, the G6PD status of every individual would be available as part of routine clinical testing. However, until that becomes a reality, we need a reliable quantitative test for G6PD activity that can be used at the point of care in areas where G6PD deficiency is prevalent. Unfortunately, such testing is not yet available.

Another important challenge is correctly diagnosing *P. vivax*, particularly in settings where microscopy is not readily available. To enable earlier diagnosis and treatment, rapid diagnostic tests for *P. vivax* that are at least as sensitive as those for *P. falciparum* are urgently needed.

The final challenge is blocking transmission. In parts of Asia where malaria persists today, transmission occurs in and near forests, where mosquitoes bite and stay outdoors. As such, they are not very amenable to house-spraying with insecticides or to the use of insecticide-treated bed nets, making it very difficult to control the vector.

Despite these challenges, several countries have either already eliminated, or are moving towards, eliminating *P. vivax* malaria, which shows that the tools we already have at our disposal can in fact not only control, but eliminate, the disease.

Do you think that the new tools could revitalize efforts to control *P. vivax* malaria?

→ Yes, I do. If we could achieve radical cure in every patient with *P. vivax*, it would have a huge impact on transmission. This is because relapses, which account for a large proportion of infections, contribute substantially to the human reservoir of infectious parasites. TQ is a newly approved single-dose radical cure that, in combination with G6PD testing, could help to deplete this reservoir. The challenge is translating this efficacious combination of interventions into a workable practical approach.

Safety is probably the single most important consideration with TQ. Even with a highly accurate test for G6PD activity, the safety of TQ depends on our ability to use it correctly. It is difficult to predict how (whether) and at what level of the healthcare system we can entrust healthworkers to use the test reliably, and to what extent countries will actually adopt and use the system. Any actual, or even perceived, adverse event related to improper use or interpretation of the G6PD test could seriously jeopardize its uptake.

What needs to be done to support the use of a G6PD quantitative test plus TQ or PQ within malaria control programmes?

→ The only way of knowing if the use of G6PD testing plus TQ or PQ is well tolerated and effective in practice is to carry out feasibility studies in a range of endemic countries that already have safety precautions in place. These experiences could then inform decisions about where in the health system these tools could be safely introduced.



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the successes and
challenges on the road
to eliminating malaria in
Southeast Asia as well
as the role of new tools
in revitalizing efforts.







Assays and anti-relapse series

With single-dose TQ now approved for the treatment of relapsing *P. vivax* malaria, it is hoped that endemic countries will soon be able to make further inroads towards elimination of the disease. However, both TQ and PQ are associated with haemolysis in patients with severe G6PD deficiency, and this means they cannot be used in pregnant women, since the G6PD status of the foetus is unknown. As such, new treatments for relapse prevention, suitable for use in all patients regardless of G6PD status, are urgently needed to support these continued efforts.

Identifying compounds active against *P. vivax* hypnozoites has proved challenging, since the parasites are difficult to access and maintain in laboratory assays. However, thanks to the efforts of the Bill & Melinda Gates Foundation liver-stage consortium and MMV's drug discovery partners, new assays to screen compounds against the liver stages of *P. vivax* malaria (including hypnozoites) are now up and running in Thailand, Cambodia and the USA, and are currently under development in India and Brazil.

In 2016, Dr Jetsumon Sattabongkot Prachumsri and her team, based at Mahidol University, Thailand, became the first research group to test 30 MMV portfolio compounds in an *in vitro* assay of *P. vivax* parasites, enabling MMV to prioritize a chemical series for which only rodent liver-stage activity was otherwise known. Data from Dr Prachumsri's assay have helped to confirm the liver-stage activity of several of MMV's translational compounds.

A separate research group, led by Prof. Dennis Kyle at the University of Georgia, USA, has developed a higher-throughput *P. vivax* liver-stage assay that uses human primary liver cells. Using sporozoites supplied by partners in Thailand and Cambodia, the team has now, for the first time in the history of *P. vivax* research, been able to screen two small-scale libraries of chemical entities, representing around 30,000 data points. Several potential radical cure molecules have been identified and chemical optimization is underway with a view to launching a full drug discovery programme. If all progresses as expected, this could potentially lead to a new clinical candidate for relapsing *P. vivax* malaria entering the malaria drug pipeline within the next 4 years. In 2019, MMV and its partners at the University of Georgia expect to deliver an additional 60,000 data points with the hope of identifying new chemical series with anti-relapse potential. ●

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